Cell Metabolism
Previews

Location, Location, Location…

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Intra-abdominal fat is an established risk factor for the metabolic syndrome. In this issue of *Cell Metabolism*, Tran et al. (2008) test the cell-autonomous and location-related properties of transplanted intra-abdominal and subcutaneous fat depots. While subcutaneous fat seems to confer metabolic benefits, species differences in adipose biology justify caution in interpreting the results.

The presence of intra-abdominal fat is an established risk factor for the metabolic syndrome in humans (Klein et al., 2007). Possible mechanisms include: (1) excess fat and associated metabolites, peptides, and hormones exert physiological consequences via the portal circulation draining to the liver; (2) cell-autonomous characteristics of adipocytes and/or other cells in the intra-abdominal depot that are independent of their anatomic location, per se; (3) increased intra-abdominal fat primarily reflects physiological stress, which is the proximate cause for the associated morbidities; and (4) limited capacity of subcutaneous depots results in deposition of excess fat in abdominal depots as well as "ectopic" sites such as liver, muscle, and islets. Deposition in the latter sites is the proximate cause of associated morbidities (Heilbronn et al., 2004). These four possibilities are not mutually exclusive (Klein et al., 2007).

In this issue, Tran et al. (2008) use fat transplantation (see Figure 1) to test the second hypothesis listed above. The authors conclude that fat depots do have cell-autonomous effects, with transplanted subcutaneous inguinal fat—but not intra-abdominal (epididymal) fat—conferring metabolic benefits. These results are consistent with, and extend, a recent report by Hocking et al. (2008).

Tran et al. (2008) transplanted as much as 1 g of fat (approximately 20% of final recipient body fat) either intraperitoneally or subcutaneously in mice, whereas Hocking et al. (2008) transplanted 300 mg; both procedures produced similar effects in the recipient. Between 10 and 12 weeks after receiving the transplants, mice with inguinal fat placed in the peritoneal cavity had less body fat and were more insulin sensitive than mice subjected to sham surgery. Subcutaneous placement of inguinal fat also affected recipient phenotypes in the same direction, but to a smaller degree than inguinal fat in the abdominal cavity. In contrast, epididymal fat transplanted either intraperitoneally or subcutaneously had no effect on body fat mass or insulin sensitivity of recipient mice.

Two tentative conclusions might be drawn from these studies. (1) Metabolic risk associated with intra-abdominal fat deposition is determined at least in part by cell-autonomous characteristics of the transplanted tissue and not by the total amount of fat present, because addition of 1 g of inguinal fat increased insulin sensitivity whereas 1 g of epididymal fat did not. (2) Anatomically distinct fat depots are phenotypically distinct (in terms of adipocyte size and metabolic and endocrine function) due to inherent cellular characteristics rather than because of differences in neural and/or blood supply to individual fat depots. A tempting extrapolation is that accumulation of subcutaneous fat is associated with lower metabolic risk than accumulation of visceral fat is, consistent with the fourth hypothesis above and a recent report of improved glucose tolerance in adiponectin-overexpressing mice that experience large increases in subcutaneous and pericardial fat (Kim et al., 2007).

Caution is in order for a number of reasons. First, experimental conditions may influence apparent effects. For example, mice receiving intraperitoneal epididymal fat transplants are more insulin sensitive than their controls when fasting, but not when fed (Konrad et al., 2007). A second, critical issue is the functional and anatomic comparability of human and rodent fat depots. A large proportion of human intra-abdominal ("visceral") fat is omental, a depot that is insignificant in rodents. The fat depots that drain into the portal circulation probably contribute most significantly to metabolic risk, though this notion has been challenged (Miles and Jensen, 2005). By these functional criteria, transplanted epididymal fat attached to the abdominal wall (Hocking et al., 2008) or interspersed within endogenous epididymal fat (Tran et al., 2008), would not be considered "visceral" fat both because of the anatomic provenance of the tissue and because of the drainage of metabolic and endocrine secretions into the systemic circulation. Epididymal fat has no precise human correspondent. Moreover, accumulating evidence suggests that epididymal fat does not respond to metabolic processes as other fat depots do. For example, epididymal fat does not increase in obese chronically decerebrate rats (Harris et al., 2006) or decrease during a short period of starvation. Transplanting fat from a portal depot might produce very different effects from those seen with epididymal fat. In particular, an interesting experiment would be transplantation of human omental and subcutaneous fat into nude mice. Finally, the transplantation of adipose tissue conveys cells other than adipocytes—e.g., resident macrophages—into the recipient animal (Weisberg et al., 2003). Tran et al. (2008) did monitor macrophage

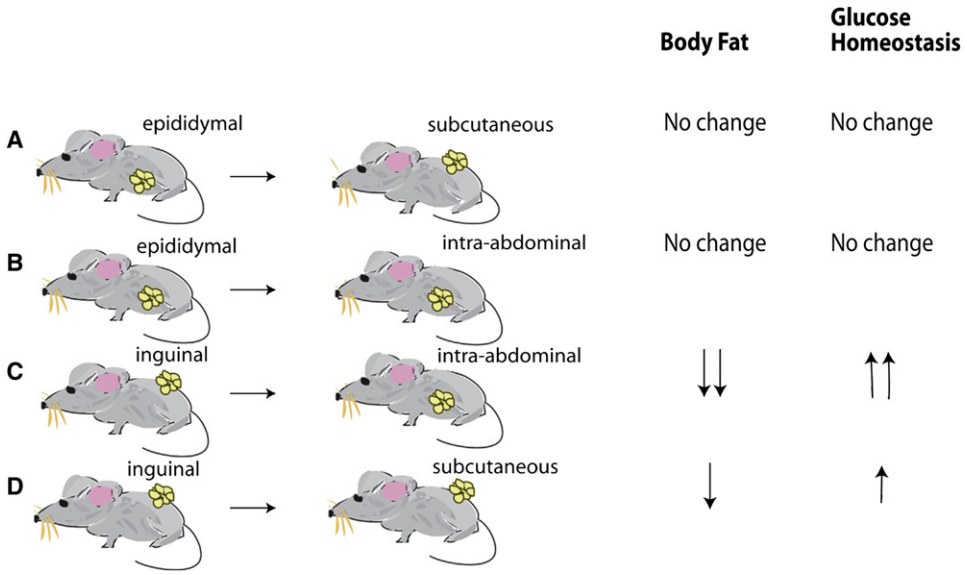

Figure 1. Schematic of Adipose Tissue Transplants

While the transplantation of epididymal (intra-abdominal) fat to either a subcutaneous or intra-abdominal depot (A and B) has little or no effect on body weight/fat gain and hepatic gluconeogenesis, transplantation of inguinal (subcutaneous) adipose tissue to either an intra-abdominal or subcutaneous depot (C and D) improves both parameters. The effect is greater for transplants to the intra-abdominal space. Prevailing notions of metabolic toxicity of intra-abdominal fat might have predicted that transplants of intra-abdominal adipose tissue, especially into the intra-abdominal depot, would result in increased body fat and deranged glucose homeostasis. The actual results are more consistent with the principle that expanding subcutaneous fat depots can defend against ectopic fat deposition and its adverse consequences in liver, muscle, and islets (Kim et al., 2007). Any extrapolation of these results to humans, however, should be made very cautiously (see text). Figure by Elizabeth Watson (Columbia University).

phenotypes, but depot differences in these cells may be more striking in humans than in mice because obese human subjects have twice as many macrophages in omental fat as in subcutaneous fat (Cancello et al., 2006).

A question unanswered by the studies of Tran et al. (2008) is the mechanism or mechanisms by which intraperitoneally transplanted inguinal fat modifies total fat mass and insulin sensitivity of mice. Surprisingly, food intake and energy expenditure were not different between the mice receiving intraperitoneal inguinal transplants and their sham controls. Yet some change in energy balance must account for the difference in weight gain observed between 8 and 12 weeks after fat transplantation. A 5 g difference in fat accumulation over a period of 4 weeks corresponds to an energy imbalance of approximately 267 kJ (Pullar and Webster, 1977), or 9.5 kJ/day; undetected small changes in energy expenditure and/or intake may account for the observed differences. Also surprising was the finding that respiratory quotient was higher in the mice that gained the least weight, indicating a preference for carbohydrate over fat oxidation. The changes in insulin sensitivity in mice with inguinal transplants were attributed to a dramatic inhibition of liver gluconeogenesis. Circulating factors and/or neural systems may modulate this apparent regulation of liver metabolism by adipose tissue. The decreased adipose adiponectin mRNA levels in the mice with improved insulin responsiveness argue against the involvement of this peptide (Pajvani et al., 2003), but the decline in resistin expression could potentially contribute to improved hepatic insulin sensitivity (Rajala et al., 2003). Whatever the identity of the fat-derived signal, it is induced in the transplant over time, because the 50% difference in fat content of mice with intraperitoneal inguinal transplants compared with other treatment groups was present at 12 weeks, but not at 8 weeks, after surgery.

Tran et al. (2008) have provided new evidence for cell-autonomous metabolic phenotypes of adipose tissue from anatomically distinct sites, with the tantalizing suggestion that accumulation of fat in subcutaneous fat depots confers metabolic benefits. These observations are consistent with the idea that expansion of subcutaneous depots can protect against ectopic deposition of excess lipids in liver, muscle, and other organs adversely affected in obesity (Klein et al., 2007; Kim et al., 2007). The increased efficacy of subcutaneous adipose tissue in the intra-abdominal space raises important questions regarding prevailing notions of primacy of position over provenance and the metabolic consequences of excess adipose tissue.

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The CAMplexities of Central Ghrelin

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The gut hormone ghrelin is known to activate hypothalamic AMPK, a crucial metabolic sensor controlling energy balance. In this issue of *Cell Metabolism*, Anderson et al. (2008) show that CaMKK2 mediates this effect by forming a unique complex of AMPKα/β with acetyl-CoA carboxylase (ACC) in a pathway distinct from the more established AMP/LKB1 pathway.

Over the last decade, attention has been focused on elucidating the role of the central nervous system (CNS) in the regulation of appetite, energy expenditure, and metabolism. Combined genetic and pharmacological manipulations have clearly defined a number of critical neural populations, signaling steps, and pathways, and the associated cellular events are now being elucidated. A central player is the adipose-specific protein leptin, which is secreted in conditions of nutrient excess and is thought to act at least in part on the neurons within the arcuate nucleus (ARC) and the ventromedial hypothalamus to modulate the expression of neuropeptides such as neuropeptide Y (NPY), agouti-related peptide (AgRP), and α-melanocyte-stimulating hormone (αMSH) to regulate food intake and metabolic events. More recently, the orexigenic (food intake-promoting) gut-derived peptide ghrelin has been shown to impact many of the same pathways. The opposing actions of leptin and ghrelin converge within the basal hypothalamus on the AMP-activated protein kinase (AMPK) system, a highly conserved sensor of cellular energy status present in all eukaryotic cells.

AMPK exists as a heterotrimeric complex of the catalytic α subunit and regulatory β and γ subunits that responds to a change in the AMP/ATP ratio. The subsequent rise in AMP results in the allosteric activation of AMPK, but it is also known to facilitate the phosphorylation of AMPK by the upstream kinase LKB1. In vitro studies of cells lacking LKB1 also have shown a basal phosphorylation and activity of AMPK, indicating the presence of an additional upstream kinase. This was identified as the Ca^{2+}/calmodulin (CaM)-dependent protein kinase kinase (CaMKK; Hawley et al., 2005). In this issue, Anderson et al. (2008) demonstrate an in vivo role for CaMKK2 in regulating hypothalamic AMPK activity.

Some of the first evidence for physiological activation of the AMPK system came from studies that reported leptin-dependent activation of the α2 isoform of AMPK in skeletal muscle (Minokoshi et al., 2002). More importantly for this discussion, hormones (e.g., leptin and insulin) and nutrients (e.g., glucose) have been demonstrated to inhibit AMPKα2 activity in the hypothalamus, an effect that correlates with the behavioral actions of central leptin, insulin, and glucose to inhibit food intake (Kahn et al., 2005). Many separate biochemical studies have now elucidated some specific substrates for AMPK (Towler and Hardie, 2007) that contributed to placing the AMPK pathway in a more physiological context (Pocai et al., 2006). Leptin, through activation of central receptors within the ARC, leads to reduced activation of AMPK, a concomitant increase in activity of acetyl-CoA carboxylase (ACC), and increased formation of malonyl-CoA. As malonyl-CoA is a key regulator of the mitochondrial enzyme carnitine palmitoyltransferase (CPT-1), this ultimately results in an increase in metabolic flux in the fatty acid synthesis pathway and decreased β-oxidation. Despite these advances, the exact mechanisms by which leptin decreases the activity of AMPK remain unknown, with their elucidation perhaps complicated by the multiplicity of signaling events emanating from activation of the leptin receptor (including PI3K, STAT2, MAPK, and Ca^{2+}; see Figure 1A).

CaMKK2 is expressed predominantly in the CNS. The growth hormone secretagogue receptor (GHS-R) is known to be coupled to Gq (thereby activating intracellular Ca^{2+}). Means and colleagues (Anderson et al., 2008) therefore postulated that the recently described actions of ghrelin to activate hypothalamic AMPK (Andersson et al., 2004) might be mediated through CaMKK2. They tested this hypothesis by generating and extensively phenotyping *CaMKK2* null mice.

Their detailed analysis of CaMKK2 expression in ARC punches of normal mice revealed an up to 20-fold enrichment